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EXAMINER	
LEAVITT, MARIA GOMEZ	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,049	KONTSEKOVA ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-37* is/are rejected.

7)☒ Claim(s) *17-37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08-14-2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 17-37 are pending.
3. The examiner acknowledges receiving a third Declaration under 37 C.F.R. § 1.132 filed on 08-14-2008; however, the declaration was unexecuted by Dr. Peter Filipcik. Furthermore, Applicants state at page 8 of remarks, "Applicants submit herewith a third Filipcik Declaration. This Declaration has been approved by Dr. Filipcik, and the executed Declaration will be submitted to the U.S. Patent Office in due course". Accordingly, the alleged evidence in the third unexecuted Declaration by Dr. Peter Filipcik submitted under 37 C.F.R. § 1.132, has been considered to the extent that the third Declaration has not been perfected yet.
4. Claims 17-37 are currently under examination to which the following grounds of rejection are applicable.

Remaining objections/ rejections in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 112 – enablement

Please, note that the scope of enablement has been expanded in view of Applicants remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing the present application, in view of the third Filipcik Declaration and further in view of reconsideration of search under different premises.

Claims 17-37 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A transgenic rat whose genome comprises a transgene comprising a DNA construct comprising a cDNA molecule, wherein:

the cDNA molecule is truncated, wherein the truncation starts at least 30 nucleotides downstream of the start codon and wherein the truncation starts at least 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein,

the cDNA molecule comprising **SEQ ID No. 9**, said cDNA operably linked to a promoter, wherein the promoter is a Thy-1 promoter,

wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology associated with Alzheimer's disease occurs in the rat when compared to normal rats,

does not reasonably provide enablement for any non-human transgenic animal .Moreover, the instant claims do not provide sufficient enablement for any promoter (e.g., constitutive or tissue specific) other than the Thy-1 promoter for the observed phenotype of neurofibrillary pathology in rat brain.

The previous Declaration signed by Dr. Peter Filipcik executed on August 1, 2007, and filed on January 10, 2007, discloses the generation of **the transgenic rat line #318** which is the same transgenic rat disclosed in the specification as filed at page 22, paragraph 2. Inventors' post-filing art by Zilka et al., (2006, FEBS Letters 580:3582-3588, submitted as exhibit 2, filed on 01-10-2007) characterizes said **transgenic rat # 318 as** containing the construct comprising nucleotides 277-999 of tau of **SEQ ID No. 3** (see page 10, paragraph 1 of Remarks filed on 09-17-2007). Therefore, the scope of enablement of the instant claims was previously modified to

the nucleotide sequence of SEQ ID No. 3, which correspond to nucleotides 277-999 encoding amino acids 93-333 (See Fig. 1 of the as-filed specification for illustrative purposes). However, in view of the 2nd Filipcik Declaration evidencing the creation of **transgenic rat # 24 as** containing the construct comprising nucleotides 277-906 of tau of **SEQ ID No. 12** (2nd Filipcik Declaration, page 2, paragraph 4) and further in view of the third Filipcik Declaration evidencing the generation of **the transgenic rat line #72** coding for 4-repeat and 3-repeat tau protein comprising nucleotides 277-999 of tau of **SEQ ID No. 3,** which is the same construct of transgenic rat # 318 (3rd Filipcik Declaration, page 2, paragraph 5), the scope of enablement has been newly modified to a tau cDNA construct comprising the nucleotide sequence of **SEQ ID No. 9.**

Reply to applicant arguments as they relate to rejection of Claims 17-37 under 35 U.S.C. 112, first paragraph, scope of enablement.

1. The transgenic non-human animal.

(a) The specification provides an enabling disclosure of how to make and use a transgenic non-human animal.

The instant claims are broadly drawn to any non-human transgenic animal, e.g., hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and others as an animal model to study Alzheimer's disease. At pages 6-8, of Remarks, Applicants content that the invention was enabling for transgenic rats as rats were created that contained both 4-repeat and 3-repeat human truncated tau as evidenced by the generation of the transgenic rat line #318 disclosed in the specification, and rat line # 24, corresponding to nucleotides 277-906, SEQ ID No. 12 in Fig. 1 (See, page 2, paragraph 4 of the Filipcik Declaration filed on 09-17-2007). In addition, Applicants argue that

the "The DNA construct used in generating transgenic rat line #24 encodes a protein, which has neurofibrillary pathology producing activity when expressed in brain cells of animals, as evidenced by the fact that transgenic rat line #24 exhibits neurofibrillary pathology. In particular, transgenic rat line #24 developed neurofibrillary lesions in the brain stem, spinal cord, primary motor cortex, and hippocampus (2nd Filipcik Declaration, para. 5). Neurological examinations showed similar features in both the #24 and #318 transgenic rat lines. For example, the onset and progression of sensory-motor impairment of animals from transgenic line #318 and transgenic line #24 is almost identical (2nd Filipcik Declaration, para. 8). Transgenic rats from line #24 were also shown to suffer from early cognitive impairment in an object recognition test (2nd Filipcik Declaration, para. 8)". Furthermore, Applicants allege that the Examiner argued incorrectly that transgenic rat line #24, which was not disclosed in the specification and is post-filing art can be relied upon to demonstrate possession of the claimed invention as "applicant can submit post-filing evidence demonstrating that the application was enabling at the time of filing. MPEP § 2164.05(b)". Moreover, Applicants refer in support transgenic animal models suitably for Alzheimer's disease to the following publications.

Hartig et al. (European Journal of Neuroscience, Vol. 25, pp. 69-80, **2007**),
Huang et al., (Brain Research 771, 1997, 213-220),
Gotz (Brain Research Reviews 35 (2001) 266-286), and
Lewis et al., (Nat Genet. 2000 Aug; 25(4):402-5).

The above arguments have been fully considered but deemed unpersuasive in relation to the claimed scope of any transgenic non-human animal.

With regard to claimed embodiments directed to a transgenic non-human animal comprising a genus of cDNA constructs coding for any N- and C-terminally truncated tau protein molecules

including sequences of SEQ ID No. 1-14 as illustrated in Fig. 1, said constructs comprising a minimally truncated tau core of **SEQ ID No. 9**, so as to generate any transgenic non-human animal having neurofibrillary pathology producing activity when expressed in brain cells of said transgenic animals, there is a high degree of unpredictability associated with the making and using of such embodiments. As Applicants argue "transgenic rat line, line #24, has neurofibrillary pathology producing activity when expressed in brain cells of animals, as evidenced by the fact that transgenic rat line #24 exhibits neurofibrillary pathology. In particular, transgenic rat line #24 developed neurofibrillary lesions in the brain stem, spinal cord, primary motor cortex, and hippocampus (2nd Filipcik Declaration, para. 7). Neurological examinations showed similar features in both the #24 and #318 transgenic rat lines. For example, the onset and progression of sensory-motor impairment of animals from transgenic line #318 and transgenic line #24 is almost identical (2nd Filipcik Declaration, para. 8). Transgenic rats from line #24 were also shown to suffer from early cognitive impairment in an object recognition test (2nd Filipcik Declaration, para. 8)". Note that neither transgenic rat line # 24 nor transgenic rat line # 72 are disclosed in the specification as filed.

Though the evidence of record provides support for three transgenic rat lines (e.g., # 24, # 72, and # 318), the guidance is not sufficient to support the present claimed invention directed to a genus of transgenic non-human animal comprising a genus of cDNA constructs coding for any N- and C-terminally truncated tau protein molecules including sequences of SEQ ID No. 1-14 as illustrated in Fig. 1, said constructs comprising a minimally truncated tau core of **SEQ ID No. 9**. How can such broadly claimed transgenic non-human animals be made and used as models for Alzheimer's disease when there is not evidence of record, at the time the invention was made, to

substantiate a reasonable correlation between non-human transgenic animals exhibiting neurofibrillary pathology producing activity as a model of Alzheimer's disease? Note that expression of the same gene in closely related rodents such rats and mice produces distinct phenotypes. For example, expression of an Amyloid Precursor Protein (APP) transgene at sufficient level to serve as a model for neurofibrillary tangles, neural lesions, Alzheimer's disease (AD) in rats produces what are referred to as "preplaques" (Echeverria, page 217, and col. 2, lines 4-9). This is in stark contrast to transgenic mice expressing APP SWE/Indiana transgenes. These mice exhibit ThioS positive fibrillar and non-fibrillar plaques, but at a much earlier age than other mice (Dudal, page 868, col. 1, parag. 1, lines 17-19 and parag. 3, lines 1-3). Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope.

In relation to the generation of any transgenic non-human animals, in addition to transgenic rats, Applicants argue at page 9-10 of Remarks that "a variety of animal models would be suitable Alzheimer's disease (AD) models since AD associated neurofibrillary (NF) pathology, based on paired helical filaments (PHF), occurs in a number of animals". Furthermore, Applicants cite the disclosures of Hartig et al. Huang et al., Gotz, and Lewis, for enablement of non-human transgenic animals demonstrating that such animals exhibit characteristics that make them suitable models for Alzheimer's disease. Such is not persuasive.

At the outset, the examiner notes that the effective filing date of the present application is **July 12, 2002.** As stated in the previous office action filed on 05-14-2008, **post-filing art of** Hartig et al. 2007, cannot be used to show what was known at the time of filing.

The MPEP 2164.05(b) referred by Applicants under the heading "Specification Must Be Enabling to Persons Skilled in the Art" recites:

> "35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected… …**The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date.** > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). **While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed.** Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered.

In addition, the **issues of enablement of the instant invention is whether a transgenic non-human animal comprising** a genus of cDNA constructs coding for any N- and C-terminally truncated tau protein molecules including sequences of SEQ ID No. 1-14 as illustrated in Fig. 1, said constructs comprising a minimally truncated tau core of SEQ ID No. 9 and exhibiting NF pathology, **can be generated without undue experimentation**. While the disclosure of Gotz (Brain Research Reviews 35 (2001) 266-286), teaches **murine models including transgenic mice** for the study of Aβ peptide containing plaques and neurofibrillary aggregates of isoforms of tau protein, the author also teaches that two mechanisms that appear to

be responsible for neurodegeneration and dementia, namely mutations in the amyloid precursors protein APP, from which the Aβ peptide is derived and Tau filament formation. Indeed, Tau in the absence of Aβ peptide production exhibit other neurodegenerative disorders including supranuclear palsy, parkinsonism linked to chromosome 17, corticobasal degeneration, and others (Abstract). Likewise, Lewis et al., teaches the pleitropic role of neurofibrillary tangles prominent not only in Alzheimer's disease but in Pick disease, progressive supranuclear palsy and corticobasal degeneration (Abstract). Clearly, NF tangles are associated with widely divergent neurodegenerative diseases in terms of their pathologic mechanisms. Conversely, the same conserve APP transgene at sufficient level to serve as a model for AD generate different phenotypes in two species of the same genus, rats and mice, as discussed in the paragraph above, reflecting the evidence that the phenotype in one specie cannot obviate an identical or even similar phenotype in the compared species. Though prior art discloses that **transgenic mice** have been used to study **NF tangles of tau protein** with aspects of histopathology and neurodegeneration associated with Alzheimer's disease, there is not evidence of record that any non-human transgenic animal other than rat was used as a model of Alzheimer's disease.

(b). ***The references cited in the action in relation to the generation of transgenic animal.***

In contrast to the Examiner arguments, Applicants allege that the Williams' reference (2000, *J. Appl. Physiol;* pp.1119-1126) is evidence that transgene expression in different species of transgenic animals is predictable. Applicants referred to the Williams' quotation, "conventional practice to deal with [variable expression] is to establish and analyze multiple lines of transgenic mice bearing any specific transgene, each of which represents a different

chromosomal event. It is mandatory for most purposed to assess at least two independent lines." (Williams, p. 1124, col. 2, 3rd paragraph). Moreover, Applicants argue that "Williams further teaches that "[i]t is a good practice to assess the effects of transgenes or knockouts in more than one mouse strain." (Williams, p. 1125, col. 1, 3rd paragraph)". As such, Applicants content that "it is routine in the art to take measures to account for potential variability in transgenic animals". Such is not persuasive.

The mere recitation that it is "conventional practice" for the skilled artisan to deal with the variability of a method to generate transgenic animals does not render the instant invention enabled, as the skilled artisan will have to engage in undue experimentation to determine unknown predictability of particular host species, specific promoter/gene combinations, random transgene insertion and genetic imprinting (e.g., transcriptional silencing of a gene based on transmission from parent to offspring of repressive nucleosomal structures) whereby NF pathology producing activity are provided for the claimed transgenic having germ and/or somatic cells (Sanders Williams et al., J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p. 1124, col. 2, paragraph 2) .

In relation to the Moreadith publication, Applicants contend that "Moreadith merely stated that this particular technology had not yet been applied to hamster, pig, sheep, cattle, rabbit, rat, mink, monkey, and humans (Summary, p. 214). Moreadith noted that as of 1997, putative pluripotential ES cell lines had been derived from each of these species and, therefore, concluded that it seemed likely that the technology would be advanced into these additional species over the next few years (Summary, p. 14)'. In addition, Applicants argue that "the presently claimed invention is not limited to the use of stem cells. For instance, in Example 2 of

the application, the employed technique was micro- injecting DNA into fertilized oozytes (not ES cells), which were afterwards implanted to the foster mother in 1 or 2-cell stage and which develop normally into the whole animal. Accordingly, any argumentation that ES cells from different organisms may have different features and might in certain cases not continue developing during embryogenesis does not mean that one could not make and use the claimed invention because the claimed invention is not limited to transgenic animals created from ES cells". Finally, Applicants argue that "Moreadith specifically states that "It]he development of transgenic technology, whereby genes (or mutations) can be stably introduced into the germline of experimental mammals, now allows investigators to create mice of virtually any genotype and to assess the consequences of these mutations in the context of a developing and intact mammal." (Moreadith (1997), Abstract) (emphasis added). In light of this statement on the state of the art, it is unclear on what grounds the Examiner is basing the argument that the current claims are not enabled with respect to transgenic mice"[emphasis added]. Such is not persuasive.

At the effective time of filing, Moreadith et al., (1997, J Mol Med pp. 208-216) clearly teaches that several putative ES cells lines have been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, but the technology was limited to mice (page 214, col. 1, paragraph 3, lines 5-12). Moreover, Moreadith et al., discloses the generation of transgenic animals e.g., "traditional gain-of function" mutation, typically created by microinjection in relation to the specific target of the gene of interest into the one celled zygote, as an art more unpredictable than the transgenic technology, wherein the gene is targeted via homologous recombination in stem cells (Abstract). Indeed, Applicants have not provided any evidence or

expectation that the claimed transgenic non-human animals generated by any transgenic technology having germ and/or somatic cells and exhibiting NF pathology producing activity is any more or less than the expectation from the teachings of Moreadith and the other prior art documents. Furthermore, in addition to Applicants' arguments in relation to the breadth of the claims to any transgenic, the claims may be interpreted to read on somatic cell gene transfer. Claim 17, as written, does not specifically convey germline transmission of the transgene and could also be interpreted as one cell in any non-human transgene animal that have been transformed with a construct comprising a nucleic acid molecule comprising a genus of cDNA molecules coding for N- and C-terminally truncated tau molecules wherein the cDNA has truncated at least 30 nucleotides downstream of the start codon and truncated at least 30 nucleotides upstream of the stop codon of the full length tau cDNA, wherein the cDNA molecule comprises SEQ ID No. 9, having a single cell expressing said protein. It would be unpredictable if expression of said transgene in a single cell of a transgenic non-human would result in collectable amount of the polypeptide so as to exhibit the claimed phenotype in the brain cells of the transgenic non-human animal. Applicants have not provided any evidence of transgenic non-human animals having solely germ cells or somatic cells exhibiting the claimed phenotype.

In relation to Keefer (2004), Applicants argue that Keefer teaches "the inefficiency of pronuclear microinjection and the unpredictability of transgene expression (Action, p. 4-5). Inefficiency and unpredictability, however, are different. Something can be inefficient and predictable. In fact, it is clear that while pronuclear transfer in cattle, sheep, and goats may be inefficient, Keefer finds it predictable to the point that Keefer teaches specific numbers of oocytes from each animal (1000, 300, and 200, respectively) that should be injected to produce 1

founder transgenic animal (Keefer, p. 6-7). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." In re Wands, 858 F.2d 731,737 (Fed. Cir. 1988). The state of pronuclear injection as described in Keefer is such that it is routine to inject a few hundred to a thousand oocytes, depending on the animal, to produce a founder transgenic animal. Thus, this is considered reasonable in the field". Such is not persuasive.

The instant issue of enablement is **whether any transgenic non-human animal comprising** a genus of cDNA constructs coding for any N- and C-terminally truncated tau protein molecules including sequences of SEQ ID No. 1-14 as illustrated in Fig. 1, exhibiting NF pathology **can be generated without undue experimentation.** Post filing art by Keefer et al., (2004, Animal Reproduction Science, pp. 5-12) clearly discloses lack of predictability on generating any transgenic animal including cows, goats and sheeps. As such, Applicant's arguments are not on point.

Finally, in so far as the disclosure of Sigmund, Applicants allege that, as in the case of Williams discussed in the paragraph above, " this variability [predictability of phenotypes in transgenic models caused by a specific genetic modification is strongly influenced by genes unlinked to the targeted locus] is a potential limitation of transgenic animals that is known to those in the art. As discussed by both Williams and Sigmund, it is routine in the art to take measures to account for potential variability in transgenic animals. As discussed above, Applicants have confirmed the phenotype of the transgenic rats with multiple lines and in different rat strains". Such is not persuasive.

As stated in the paragraph above, Applicants have not provided any evidence or expectation that the claimed transgenic non-human animals generated by any transgenic technology having germ and/or somatic cells and exhibiting NF pathology producing activity is any more or less than the expectation from the teachings of Sigmund and the other prior art documents. Hence Applicant has presented insufficient evidence commensurate with the scope of the claims. Thus, given the paucity in the art regarding the claimed transgenic-human animal comprising a construct expressing a truncated tau protein one skilled in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

Promoters

In relation to Applicant's argument to enabling issues related to the need of a construct operationally linked to a promoter that will allow for the expression of the gene of interest in the brain cells at an appropriate level, Applicants contend at pages 16-18 of Remarks, that " expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter is further unavailing because claim 17 does not recite a promoter and does not need to" as " Expression of a gene of interest in a transgenic animal requires many well-known things including, for example, numerous components for transcription and translation of the gene". Moreover, Applicants allege," numerous promoters are known and readily available to those in the art. Examples of some promoters that have been used to drive transgene expression in the central nervous system of various mammals are provided in the review article by Fitzsimons et al (Methods 28:227-236 (2002); see e.g., Tables 1 and 2). The cytomegalovirus (CMV) promoter, for example, had been used to drive the expression of several different transgenes in the central

nervous system of rat, mice, and monkeys (Fitzsimons, Table 1). In addition, the publication by Lewis et al. (Nat Genet. 25(4):402-5 (2000)) shows the expression of human tau protein in mice using the mouse prior promoter (MoPrP)". Such is not persuasive.

Claims 17-36 are drawn to a transgenic non-human animal whose genome comprises a transgene comprising a DNA construct encoding a N- and C-terminally truncated human tau, the cDNA molecule comprising **SEQ ID No. 9.** The claims, as written, do not require the cDNA molecule to be linked to a promoter for efficient expression. The specification provides insufficient guidance for one skilled in the art to make and use the claimed constructs for efficient expression of the N- and C-terminally truncated human tau as claimed. For the reasons already discussed in the previous office action, the art clearly sets forth the required linkage of a gene to a promoter for expression of said gene. The as-filed specification provides guidance or evidence for how to make and use the Thy-1 promoter for the observed phenotype of neurofibrillary pathology in rat brain; however, the claims do not recite such a structural limitation. For the reasons already discussed in the previous office action, the art clearly set forth in the art the required linkage of a gene to a promoter for expression of said gene. Given that gene expression from a construct comprising a nucleic acid not operably linked to a nucleic acid was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to tau protein expressed from a construct as recited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability using an expression vector missing a promoter as a promoter is necessary for the gene expression. In so far as the use of any promoter (e.g., constitutive or tissue specific) other than the Thy-1 promoter for the observed

phenotype of neurofibrillary pathology in rat brain, as recited in claim 37, the art clearly teaches that no all promoters result in efficient expression or expression at levels in the appropriate target tissue to result in a phenotype that is useful. For example, use of a CMV promoter which is active in a wide range of tissues and drives high-level constitutive expression will generate a transgenic non-human animal exhibiting global expression of the truncated tau gene that will necessarily result in a different transgene phenotype. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

New grounds of objection

Claim Objection

Claims 17-37 are objected to because of the following informalities. Claim 17 and 37 recite, "the molecules have truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence". It is unclear whether the first 30 nucleotides of the full length tau cDNA sequence downstream the start site are truncated or the truncation begins at the 30 nucleotide position downstream of the start codon. Similarly, it is unclear whether the truncation 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence includes the 30 nucleotides upstream of the stop codon or the truncation begins at the 30 nucleotide position upstream of the stop codon. Appropriate correction is required.

Drawings objection

The Drawings submitted by Applicants and filed on 08-14-2008 comprising Figs. 1-9 are objected to because of the following reasons. Initial drawings filed on 01-12-2005 corresponding to Figures 1-10 do not correspond to the content of Figs. 1-9 filed on 08-14-2008. The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. Applicant is required to furnish a drawing under 37 CFR 1.81(c). No new matter may be introduced in the required drawing. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d).

Specification objection

The amendment filed 08-14-2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. Though transgenic rat line #318 was disclosed in the specification as filed, transgenic rat lines #24 and #72 and their corresponding phenotypes are not. For example, Figures 7 and 8 illustrate that truncated tau expression was not dependent on genetic background, specifically the tau transgene was transferred from the genetic background of the hypertensive SHR strain (Tg line #72) into the normotensive Wistar strain (WKY) an almost identical phenotype at the level of biochemical examination and behavioral measurements was observed (Remarks page 8; 3rd Filipcik Declaration, para. 12 and Figures 6 and 7). Moreover, Fig 8 illustrates the generation of transgenic rats comprising both the 4-repeat and 3-repeat human truncated tau and its phenotype. The disclosure of transgenic line SHR24/72 is not supported by the teachings of the specification as filed. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material

which is not supported by the original disclosure is as follows: The Drawings submitted by Applicants filed on 08-14-2008 comprising Figs. 1-9 do not correspond to the content of Figs. 1-9 filed on 08-14-2008 and are not supported by the disclosure of the Specification as filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

Claims 17-37 are rejected.

Other art for Comment

The following are cited to complete the record.

a) Dudal et al., Inflammation occurs early during the Abeta deposition process in TgCRND8 mice. Neurobiol Aging. 2004 Aug;25(7):861-71.
b) Echeverria et al., Rat transgenic models with a phenotype of intracellular Abeta accumulation in hippocampus and cortex. J Alzheimers Dis. 2004 Jun;6(3):209-19

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Michael Burkhart/
Primary Examiner, Art Unit 1633

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